REMARKS

Claims 1-37 are active. New Claim 37 finds support in the specification at page 3, lines 9 and 10 from page bottom. Accordingly, the Applicants do not believe that any new matter has been added.

Restriction/Election

Claims 2, 3, 10-18 and 21-31 have been withdrawn from consideration. It is the Applicants understanding that these claims may be rejoined and examined upon an indication of allowability of the claims in the elected Group. The present rejections are directed to the generic claims, as indicated in the "Status of the Application" section of the Official Action.

Allowable Subject Matter

The Applicants thank Examiner Sheikh for indicating that claims directed to the elected species (nicorandil and poly(vinylalcohol) would be allowable. The Applicants respectfully submit that the subject matter of new Claim 37 should also be allowable.

Rejection--35 U.S.C. 102

Claims 1, 4-6, 19, 20 and 32-36 were rejected under 35 U.S.C. 102(b) as being anticipated by Pfister et al., U.S. Patent No. 5,232,702. These claims are not anticipated by Pfister, because Pfister does not disclose a "medicine storage layer comprising one or more medicines that permeate, dissolve, disperse or diffuse into a plasticized permeation control film which has been activated by moisture" as required by Claim 1.

Col. 2, lines 5-45 are cited as disclosing the invention. This section of the Pfister describes silicone pressure sensitive adhesive compositions comprising a silicone fluid, a silicate resin and a cohesive strengthening agent, see lines 10-12. Lines 18-30 indicate that the cohesive strengthening agent may be selected from compounds, including poly(vinylalcohol). However, this section does not describe all the elements of the composition of Claim 1, such as the medicine storage layer or permeation controlling film.

Col. 5, lines 25-40, were cited as disclosing the invention. This section of Pfister describes a cohesive strengthening agent, including polyvinylalcohol, but does not describe all the elements of the composition of Claim 1, such as the medicine storage layer or permeation controlling film.

Col. 8, lines 28-68, and col. 9, lines 1-23, were cited as disclosing the invention. These sections of Pfister describe the drug delivery devices of Figs. 3 and 4. The Applicants respectfully request that the Office specifically address the remarks regarding the devices of Figs. 3 and 4 set forth in their prior response. For the convenience of the Examiner, these remarks are reiterated and elaborated upon below.

As shown in Fig. 3, the liquid reservoir device of Pfister contains a liquid reservoir (30) instead of the present invention's medicine storage layer comprising one or more medicine(s) that permeate, dissolve, disperse or diffuse into a plasticized permeation control film once it has been activated by moisture. The Applicants submit that the "medicine storage layer" of the present invention as described on pages 4-6 of the specification is clearly distinguishable from the "liquid reservoir" or Pfister. However, assuming *arguendo*, that these terms were construed as being synonymous, Pfister does not describe a medicine storage layer that permeates, disperses, or diffuses into a plasticized permeation control file that has been activated by moisture as required by Claim 1.

Fig. 4 of Pfister shows a solid reservoir system that may optionally contain a "rate controlling membrane", see col. 9, lines 15-16. However, this term appears to be merely functional, as there is no description of what a rate controlling membrane is. Pfister does not provide a description of what type of substance a rate controlling membrane is made from and his examples do not refer to rate controlling membranes. The Applicants submit that in the art, generally, a rate controlling membrane comprises polyethylene, polyvinyl acetate or ethylene-vinyl acetate copolymers--see U.S. Patents Nos. 5,411,740, 5,451,407, 5,462,745, 6,248,348 and 6,267,984. Sections of these patents are attached to this response for the convenience of the Examiner.

Unlike Pfister, which does not describe the composition of the rate controlling membrane, the specification describes the permeation controlling film of the present invention as containing substances, such as poly(vinylalcohol). Claim 1 requires that this film be plasticized when activated by moisture. Claims 10-13 enumerate specific substances for this film. While Pfister et al. disclose the use of poly(vinyl alcohol), poly(vinylpyrrolidone), and polysaccharides such as cellulose and methylcellulose (see column 2, lines 18-30; column 5, lines 25-40; column 6, lines 24-33; Claims 5, 9, 1.4, 17 and 20), these substances are used as cohesive strengthening agents and are contained in the adhesive. On the other hand, substances, such as poly(vinylalcohol) of the present invention are contained in the permeation controlling film, see Claims 2 and 3, the Specification, page 4, lines 20-28.

Moreover, even if Pfister adequately described a rate controlling membrane, and the permeation control film of the present invention were deemed to be one type of a rate controlling membrane, Pfister does not disclose a permeation controlling film that is plasticized when activated by moisture from the skin and that permits the permeation of the

medicine(s) out of the medicine storage layer when plasticized. On the other hand, the present invention comprises percutaneous absorption preparations, more particularly reservoir type percutaneous absorption preparations, wherein at the time of preservation the permeation controlling film is impermeable to medicines and the medicines exist stably in a medicine storage layer. At the time of application of the preparation, as the permeation controlling film is plasticized by moisture evaporating from the skin, the medicines move into a layer of an adhesive and are absorbed through the skin, see the Specification, page 1, Technical Field.

Accordingly, Pfister does not teach all the elements of the present invention, for instance, the permeation control film of Claim 1. Pfister also does not describe the particular materials used for the permeation control films of Claims 2, 3 and 10-13.

Similarly, the present invention is not obvious over the cited art because there is no suggestion in Pfister to make a device comprising a permeation control film that once moistened by the skin allows a medicine to permeate and pass through the film to the skin. Unlike the permeation control film of the present invention, a rate controlling membrane comprising polyethylene, ethylene-vinyl acetate copolymer, or the like, is not plasticized by moisture volatilized from the skin at the time of application of the preparation.

Therefore, the Applicants respectfully request that this rejection be withdrawn, because Pfister et al. neither disclose nor suggest a permeation controlling film (rate controlling membrane) that is plasticized when activated by moisture, such as a water-soluble polymer including poly(vinyl alcohol), poly(vinylpyrrolidone) or polysaccharides.

Moreover, assuming *arguendo*, that the rate controlling membrane of Pfister was deemed to be equivalent to the permeation control film of the present invention, there is no suggestion in Pfister of the superior properties of the present invention compared to conventional rate controlling membranes. As shown in the attached Declaration of Mr.

Kaname Nakahara (see e.g. the graph on page 3), the composition of the present invention in the form of percutaneous absorption preparation, which comprises a permeation control film that is plasticized and activated by moisture, is remarkably superior in permeability of drug compared to a similar percutaneous absorption preparation with a conventional rate controlling membrane comprising polyethylene or ethylene-vinyl acetate copolymer.

For all of the above reasons, the Applicants respectfully request that this rejection be withdrawn.

Rejection--35 U.S.C. 103

Claims 1, 4-8, 19, 20 and 32-36 were rejected under 35 U.S.C. 103 (a) as being unpatentable over Pfister et al., U.S. Patent No. 5,232,702. As discussed above, the cited prior art does not disclose or suggest the present invention.

Rejection--35 U.S.C. 103

Claim 9 was rejected under 35 U.S.C. 103(a) as being unpatentable over Mantelle, U.S. Patent No. 5,446,070. The invention of Claim 9 is not obvious over Mantelle, because this patent neither discloses nor suggests the composition of Claim 9. Mantelle, col. 4, lines 25-44, describes a bioadhesive comprising an active agent, a solvent, and polysaccharide bioadhesive carrier. Col. 12, lines 10-15, describe an anesthetic agent dissolved in a solvent which is added to an adhesive and placed on a flexible form or backing. Col. 41, line 17 describes the drug nicorandil.

Mantelle does not describe or suggest a composition comprising supporting body, a

medicine storage layer or a permeation control film that is activated by moisture, an adhesive and a release liner. Specifically, Mantelle does not suggest using a water-soluble polymer to form a permeation control layer. Accordingly, the Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In view of the above amendments and remarks, the Applicants respectfully submit that this application is now in condition for allowance. Early notification to that effect is earnestly solicited.

Respectfully submitted,

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MARKED UP COPY OF AMENDMENT

Add new Claim 37:

--37. (New)--

The *rate-controlling membrane* may be fabricated from permeable, semipermeabl or microporous materials which ar known in the art to control the rate of agents into and out of delivery devices and having a perm ability to the permeation enhancer lower than that of oxybutynin reservoir 12. Suitable materials include, but are not limited to, poly thylen , polyvinyl acetate and ethylene vinyl acetate copolymers.

Th *rate-controlling membrane* may be fabricat d from permeable, semipermeable or microporous materials which are known in the art to control the rate of agents into and out of delivery devices and having a perm ability to the permeation enhancer lower than that of drug reservoir 12. Suitable materials include, but are not limited to, polyethylene, polyvinyl acetate and ethylene vinyl acetate copolymers.

EXAMPLE 1

Transdermal delivery devices for the controlled delivery of dexsecoverine were prepared utilizing Dow Corning DC 355 silicone adh siv as the highly permeable medical adhesive, low density polyethylene (LDPE) or ethylene vinylacetate (EVA) copolymer (9% VA) as the ***rate controlling membrane,*** EVA (40% VA) as the non-diffusible drug reservoir diluent, pigmented medium density polyethylene/aluminized polyester as the impermeable backing member and racemic secoverine or dexsecoverine as the source of dexsecoverine. Secoverine and dexsecoverine are extremely soluble (essentially miscible) in the EVA (40% VA) diiuent and thus the weight percent concentration in the diluent corresponds approximately to the thermodynamic activity. Secoverine and dexsecoverine are solvents for DC355 and form solutions therewith at concentrations of at least 300 mg/cm.sup.3 and adverse effects were observea when the concentration reached about 50 mg/cm.sup.3. Thus according to the preferred dexsecoverine delivering embodiments of this invention, it is desirable to maintain the agent concentration in the adhesive below about 45 mg/cm .sup.3 which corresponds to an activity of about 0.15 in the drug reservoir and the adhesive layers. The thicknesses of the adhesive and rate controlling layers in the subsaturated system were selected to provide an initial pulse of about 225 .mu.g/cm.sup.2 to saturate the agent binding sites in the skin, the contribution to the pulse of each such layer being dependent on the thickness of the layer and the solubility of the agent in each layer. A thicker layer would provide a higher initial pulse and a thinner layer would provide a smaller initial pulse for the same initial activity. One or 1.3 .mu.l LDPE and 2 or 4 mil EVA (9% VA) rate control membranes were utilized in the preferred embodiments, and drug reservoirs of approximately 5-20 mils were tested. A 5 mil thickness was sufficient to prevent the activity of the agent in the reservoir 3 from decreasing by more than 30% during a four-day administration period. The in vitro release rates of various subsaturated dexsecoverine systems are compared to the characteristics for unit activity systems in Table I. FIG. 3 shows the in vitro release rates at 32.degree. C. directly into an infinite sink and through cadaver skin into an infinite sink from racemic secoverine systems and illustrates the effect of varying reservoir thicknesses on in vitro release rates.

The *rate-controlling membrane* may b fabricated from permeabl , semipermeable or microporous materials that are known in the art to control the rate of agents into and out of delivery devices. Suitable materials includ , but are not limited to, high d nsity polyethylene, low density polyethylene, polyvinyl acetat , polypropylene and ethylene vinyl acetate copolymers.

The *rate-controlling membrane* 13 may be fabricated from permeable, semipermeable or microporous materials which ar known in the art to control the rate of agents into and out of delivery devices and having a permeability to the permeation enhanc r lower than the matrix material of zone 12. Suitable mat rials include, but are not limited to, polyethylene, polyvinyl acetate and ethylene vinyl acetate copolymers.

12/declaration
1.132

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of

KANAME NAKAHARA et al. Atty. Docket No.: 216208US0XPCT

Serial No. 09/762,615 Group: 1615

Filed: February 8, 2001 Examiner: SHEIKH, HUMERA N

For: A MOISTURE-SENSITIVE PERCUTANEOUS ABSORPTION PREPARATION

DECLARATION PURSUANT TO 37 C.F.R.1.132

1. I, Kaname Nakahara, do hereby declare as follows:

I graduated from Tohoku University in March, 1997. Since April, 1997, I have been employed by Lintec Corporation.

I have a full knowledge of the present invention and cited references.

2. In order to demonstrate the patentability of the present invention, the following experiment was carried out in the manner described in Example 1 and Test Example 2 of the specification of the present application.

Production of percutaneous absorption preparations

To 100 parts by weight of an acrylic adhesive (PE-300, made by Nippon Carbide Ind.) there was added 4.0 parts by weight of a crosslinking agent (CK-101, made by Nippon Carbide Ind.), and ethyl acetate was added so as for the weight of the solids per the total weight to make 40 % by weight. The mixture was fully stirred with a Disper to prepare a uniform solution. This solution was coated

uniformly on a release film comprising a 38 μm thick poly(ethylene terephthalate) film and dried for 4 minutes in a drying oven of 80℃ to form a layer of adhesive having a coating amount of 38 g/m^2. Then, a polymer (poly(vinyl alcohol) (PVA), polyethylene (PE) or ethylene-vinyl acetate copolymer (EVA)) film having a thickness of 30 μm was affixed on the layer of adhesive.

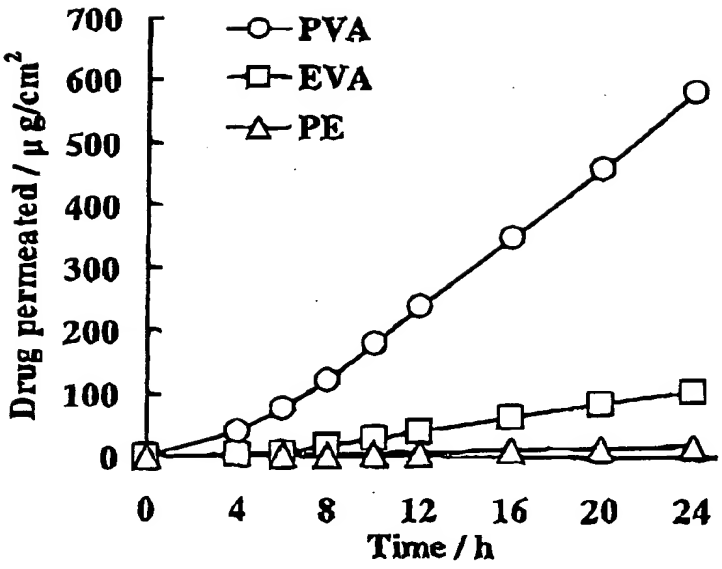
Nicorandil of 10 parts by weight was dissolved in 90 parts by weight of methanol to prepare a solution having a nicorandil concentration of 10 %(w/w). This solution was coated uniformly on a 50 μm thick poly(ethylene terephthalate) film and dried for 1 minute in a drying oven of 60℃, and the medicine storage layer was formed so as for the content of nicorandil to become about 500 mg/m^2.

This film was attached to the previously prepared the polymer film, layer of adhesive and release liner to produce a percutaneous absorption preparation.

Evaluation of percutaneous absorbability

Using the percutaneous absorption preparations obtained above, the percutaneous absorbability was evaluated according to the following method.

A 8-week-aged male Wistar rat (body weight 170-190 g) was strangled, and the skin of its abdomen was taken out after removal of the hair with a hair clipper and a shaver. After the fat on the cutis side was removed with a forceps, the horny layer side, to which the percutaneous absorption preparations were attached, was applied to a vertical type diffusion cell (cell volume:4.0 ml, effective diffusion area: 0.95 cm^2) being kept in advance at 37℃. To the cutis side an isotonic phosphate buffer having a pH of 7.4 was applied, and the permeation experiment was conducted. During the experiment the star-head type stirring piece put in the cell of the cutis side was stirred by a magnetic stirrer. A predetermined amount of sample was taken with the lapse of time and added to acetonitrile containing an internal standard substance, and the medicine that had permeated was determined with a HPLC. The following figure shows cumulative permeation amounts of the medicine at the times up to 24 hours from the beginning of the permeation test.



As seen from the figure, the percutaneous absorption preparation of the present invention is remarkably superior in permeability of drug to a percutaneous absorption preparation with a conventional rate controlling membrane comprising polyethylene or ethylene-vinyl acetate copolymer.

Accordingly, the present invention is patentable over the cited references.

3. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: This 4th day of November, 2002

Kaname Nakahara

Kaname Nakahara